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Antisynthetase syndrome: Pulmonary computed tomography findings of adult patients with antibodies to aminoacyl-tRNA synthetases

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ABSTRACT

Objectives: To describe the pulmonary CT findings in patients with anti-ARS-antibody-positive interstitial lung disease (anti-ARS-ILD)

Methods: The CT findings of 64 patients with anti-ARS-ILD were retrospectively reviewed. The images were retrospectively reviewed independently by 2 chest radiologists, and the final decision on the CT findings was made by a third chest radiologist.

Results: There were 16 male and 48 female patients, aged 54.2 ± 13.4 years. Sixteen patients had anti Jo-1, 24 had anti-EJ, 9 had anti-PL-7, 7 had anti-PL-12, 5 had anti-KS, and 3 had anti-OJ antibodies. Overall, 63 patients (98.4%) had CT findings predominantly in the lower lobe; 61 patients (95.3%) showed peripheral opacities, and 47 patients (73.4%) showed peribronchovascular opacities. Ground-glass attenuation, consolidation, and reticulation showed similar distribution patterns. Regarding detailed CT findings, 89.1% of patients had lower volume loss, 76.6% had interlobular septal thickening, and 67.2% had thickening of bronchovascular bundles. The final radiologic diagnoses were as follows: inconsistent with usual interstitial pneumonia (UIP) in 63 patients (98.4%), which included nonspecific interstitial pneumonia (NSIP) in 35 patients (55.6%), organizing pneumonia (OP) in 4 patients (6.3%), and OP with fibrosis in 22 patients (34.9%).

Conclusions: The characteristic CT findings of patients with anti-ARS-ILD were areas of ground-glass attenuation and reticulation, predominantly distributed as lower and peribronchovascular lesions, which is compatible with NSIP. One-third of patients showed OP with fibrosis.

1. Introduction

Myositis has long been known as a connective tissue disease that is frequently associated with interstitial lung disease. Pleural irregularities and prominent parenchymal interlobular septa, ground-glass attenuation, patchy consolidation, parenchymal bands, irregular peribronchovascular thickening, and subpleural lines have been commonly found on the chest computed tomography (CT) [1,2]. Some cases also show honeycombing on CT [3].

Patients with myositis were recently subclassified according to various myositis-related antibodies, including antiaminoacyl-tRNA synthetase (ARS) antibodies, anti-MDA5 antibody, and anti-TIF1 antibody, by investigators using immunoprecipitation assays [4]. Both the clinical and imaging features of each subclass of myositis can be different.

Antibodies against ARS, a family of cytoplasmic enzymes, have been shown to be highly specific for polymyositis and dermatomyositis (PM/DM) and strongly associated with interstitial lung diseases (ILDs) [4–7]. Anti-ARS antibodies include antihistidyl- (anti-Jo-1), antiglycyl- (anti-EJ), antithreonyl- (anti-PL-7), antialanyl- (anti-PL-12), antiisoleucyl- (anti-OJ), antiasparaginyl- (anti-KS), antiphenylalanyl- (anti-Zo), and antityrosyl-tRNA synthetases. Several studies have reported on the clinical, radiologic, and pathologic pulmonary manifestations of patients with anti-ARS-antibody-positive (anti-ARS)-ILD. Anti-ARS-ILD was not uncommon in patients with idiopathic interstitial pneumonias (IIPs) [8],

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Table 1
Patinet characteristics.

Age	54.2 ± 13.4			
Sex	Male	16	Female	48
Smoking history	Yes	23	No	41
Symptoms	Myositis	36		
	Arthritis	23		
	Mechanic's hands	16		
	Fever	18		
	Raynaud's phenominon	17		
	ILD	64		
Anti-ARS antibodies	Jo-1	16		
	EJ	24		
	PL-7	9		
	PL-12	7		
	OJ	3		
	KS	5		
Diagnosis	IIP	23	CTD	41
			PM	9
			DM	24
			MCTD	2
			DM + SSc	1
			SSc	1
			Sjs	1
			RA	1
			PM + Sjs + RA	1
			SSc + RA + Sjs	1

IIP, idiopathic interstitial pneumonia; CTD, connection tissue disease; PM, polymyositis; DM, dermatomyositis; MCTD, mixed connective tissue disease; SSc, systemic screrosis; Sjs, Sjögren syndrome; RA, rheumatoid arthritis.

Table 2
Frequencies of the various CT findings.

CT finding	Number of patients	κ
Ground-glass attenuation	63/64 (98.4)	−0.03
Air-space consolidation	31/64 (48.4)	0.69
Reticulation	43/64 (67.2)	0.48
Honeycombing	2/64 (3.1)	0.79
Subpleural sparing	21/64 (32.8)	−0.10
Interlobular septal thickening	49/64 (76.6)	0.07
Thickening of bronchovascular bundles	43/64 (67.2)	0.13
Pleural thickening or irregularity	29/64 (45.3)	0.12
Nonseptal linear opacity	22/64 (34.4)	0.11
Subpleural curve-linear shadow	24/64 (37.5)	0.28
Cyst	9/64 (14.0)	0.23
Enphysema	14/64 (21.9)	0.47
Lower volume loss	57/64 (89.1)	0.48
Predominant overall anatomic distribution		
Peripheral	61/64 (95.3)	0.14
Peribronchovascular	47/64 (73.4)	0.37
Diffuse	1/64 (1.6)	−0.02
Random	1/64 (1.6)	N.A.
Dependent	1/64 (1.6)	N.A.
Overall zonal predominance		
Lower	63/64 (98.4)	0.32
Diffuse or Random	1/64 (1.6)	1.00

and patients with anti-ARS-ILD had common clinical pulmonary manifestations, regardless of the presence of PM/DM [9]. Patients with anti-ARS-ILD usually have a chronic clinical course, nonspecific interstitial pneumonia (NSIP) and/or organizing pneumonia (OP) patterns on pulmonary CT, and a good response to corticosteroid treatment [10,11].

However, the detailed CT findings of patients with anti-ARS-ILD are still unknown. The aim of this study was to clarify and describe the CT findings of patients with anti-ARS-ILD.

2. Patients and methods

2.1. Study population

Our institutional review boards approved this retrospective study. We reviewed the medical records in our database of all the patients seen in 2 institutions, who were identified with anti-ARS-ILD during the previous 10 years. Anti-ARS-ILD patients were identified using the following criteria: diagnosed with ILD on chest CT; positive for anti-ARS antibody; and without any other disease manifesting abnormalities on chest CT, including sarcoidosis, pulmonary infection, lymphoproliferative disease, lung cancer, and hypersensitivity lung disease. Anti-ARS antibody was detected by immunoprecipitation assays [4] or enzyme-linked immunosorbent assays (ELISAs) [12].

2.2. Examination and assessment of high-resolution (HR) CT scans

HRCT examination of patients with anti-ARS-ILD was performed during the initial work-up. HRCT data acquisition was obtained at end inspiration with the patient in the supine position, using a variety of CT systems. The protocols consisted of 1- or 2-mm collimation sections reconstructed using a high-spatial-frequency algorithm at 1- or 2-cm intervals. The images were read at window settings appropriate for viewing the lung parenchyma (window level −600 to −700 Hounsfield units [HU], window width 1200 to 1500 HU) and the mediastinum (window level 400–500 HU, window width 20–40 HU).

The images were retrospectively reviewed independently by 2 chest radiologists with 15–27 years of experience. Final decisions on the findings were reached by a third chest radiologist with 15 years of experience. The radiologists were aware that the patients had anti-ARS-ILD, but were blinded to any other clinical findings or patient outcome. Radiologists identified and further evaluated the CT findings, including the extent of spared areas, as follows: ground-glass attenuation, air-space consolidation, honeycombing, intralobular reticular opacities, emphysema, traction bronchiectasis, and the presence of subpleural sparing and upper lobe subpleural irregular lines. The definitions of these CT findings were based on the literature, as follows: ground-glass attenuation was defined as hazy, increased attenuation that did not obscure the underlying vessels, and was further characterized as with or without traction bronchiectasis; air-space consolidation was defined as homogeneous increase in pulmonary parenchymal attenuation; honeycombing was defined as clustered cystic air spaces with well defined and thick walls, ranging from several millimeters to 1 centimeter, seen in the subpleural regions; intralobular reticular opacities were defined as irregular and randomized linear shadows separated by a few millimeters; traction bronchiectasis was defined as irregular bronchial dilatation within or around areas with parenchymal abnormalities; subpleural sparing was defined as an area of relative sparing adjacent to the pleura in the presence of fibrotic changes in the lung field; and upper lobe subpleural irregular lines were defined as irregular lines adjacent to the pleura in the upper lobes [13–15].

The extent of CT findings was evaluated separately for 6 pulmonary zones (upper, middle, and lower in each side). The borders between the upper, middle, and lower lung zones were divided by the level of the tracheal carina and the inferior pulmonary vein, respectively. The radiologists estimated the percentage of lung with abnormalities in each of the zones, which included spared areas, ground-glass attenuation with and without traction bronchiectasis, air-space consolidation, honeycombing, intralobular reticular opacities, and emphysema. The percentage of whole lung involved

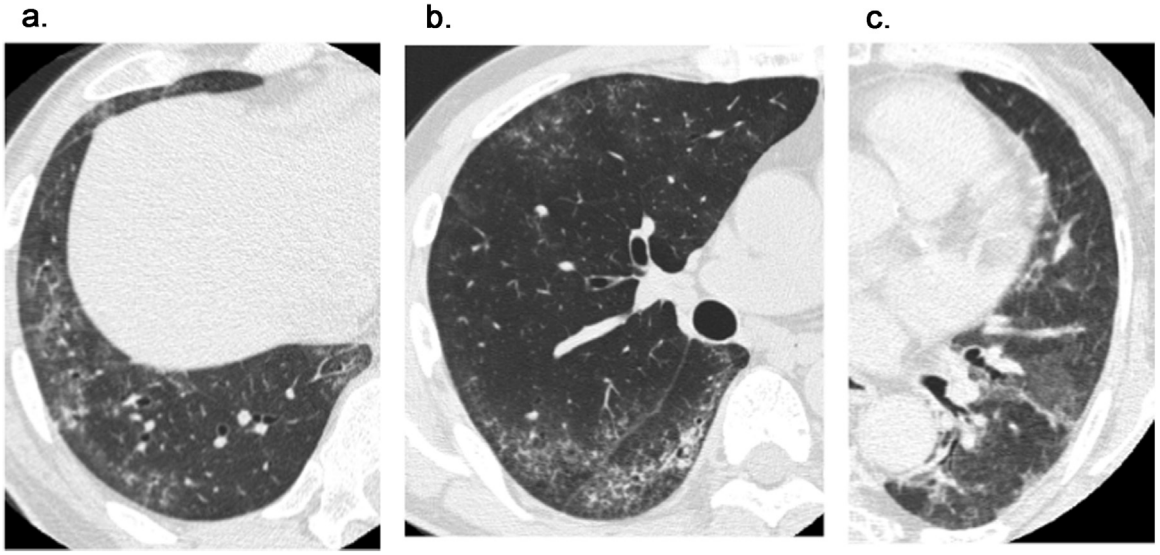

Fig. 1. Ground-glass attenuation. (a) Thin-section CT scan of the right lung in a 44-year-old man with ARS-ILD (EJ) shows areas with ground-glass attenuation in peripheri. (b) Thin-section CT scan of the right lung in a 50-year-old man with ARS-ILD (KS) demonstrates areas with ground-glass attenuation in both peripheral and peribronchovascular regions. (c) Thin-section CT scan of the left lung in a 50-year-old man with ARS-ILD (KS) depicts areas with ground-glass attenuation in peribronchovascular regions.

with abnormalities was calculated by determining the mean of the percentages of involved lung in each lung zone.

Traction bronchiectasis was evaluated by summing the number of pulmonary segments with traction bronchiectasis. Subpleural sparing and upper lobe subpleural irregular lines were evaluated as absent or present. The radiologists also determined the predominant distribution of CT findings and whether or not the distribution was asymmetric. The predominant distribution of findings was classified as lower, peripheral, or peribronchovascular. Asymmetrical distribution was assessed as asymmetric extent or progression.

The final radiological diagnosis was based on the criteria of the ATS/ERS/JRS/ALAT guidelines [16]. Findings inconsistent with the usual interstitial pneumonia (UIP) pattern were classified as: "any further pattern". OP with fibrosis was identified on the CT of patients who showed regions of air-space consolidation bilaterally, predominantly in the lower lung zones, and loss of volume.

2.3. Statistical analysis

Statistical analysis was performed using statistical software (SPSS 12.0J, 2003; SPSS Inc. Chicago, IL). Interobserver agreement regarding the presence/absence of CT findings and overall impression of the findings was analyzed by calculating the kappa statistic [17] on the assessments made prior to agreement by consensus. Interobserver agreement was classified as follows: poor

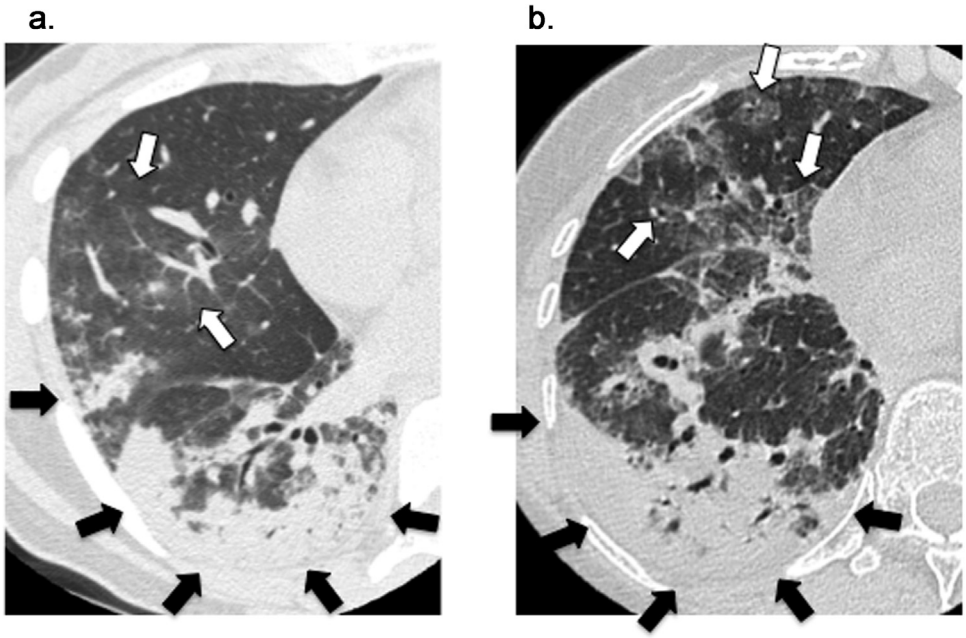

Fig. 2. Airspace consolidation. (a) Thin-section CT scan of the right lung in a 43-year-old woman with ARS-ILD (EJ) shows areas of airspace consolidation in peripheral and peribronchovascular regions (black arrows). Areas with ground-glass attenuation are seen around those of airspace consolidation (white arrows). (b) Thin-section CT scan of the right lung in a 66-year-old man with ARS-ILD (Jo-1) presents areas of airspace consolidation in peripheral and peribronchovascular regions. Areas with ground-glass attenuation are also seen (white arrows).

(κ = 0–0.20), fair (κ = 0.21–0.40), moderate (κ = 0.41–0.60), substantial (κ = 0.61–0.80), and almost perfect (κ = 0.81–1.00).

3. Results

Table 1 shows the characteristics of the patients included in the study. There were 16 men and 48 women, aged 54.2 ± 13.4 years (mean ± SD) (range 18–79 years). Twenty-three patients were current smokers or former smokers. The following types of anti-ARS antibodies were detected: anti-Jo-1 in 16, anti-EJ in 24, anti-PL-7 in 9, anti-PL-12 in 7, anti-OJ in 3, and anti-KS in 5 patients. The following disorders were definitively diagnosed: 23 patients with IIP; and 41 with connective tissue disease (CTD) (36 patients with PM/DM [2 of these patients also had another CTD] and a few patients with mixed connective- tissue disease [MCTD], scleroderma, Sjögren syndrome, and rheumatoid arthritis). With regard to prognosis, 46 patients were alive, 5 patients were died, and 13 patients were unknown. Regarding interpretations of CT findings, interobserver agreement for each of the CT abnormalities ranged from poor to substantial (κ = −0.10–0.79) (Table 2). Interobserver agreement for predominant overall anatomic distribution and overall zonal predominance ranged from poor to perfect (κ = −0.02–1.00). Interobserver agreement regarding the diagnosis of UIP based on the criteria of the ATS/ERS/JRS/ALAT guidelines [16] was moderate, and was substantial regarding the final diagnosis.

The frequencies of the various CT findings are summarized in Table 2. All anti-ARS-ILD patients presented with bilateral abnormal shadows; bilateral areas with ground-glass attenuation were found in 63 (98.4%) of 64 patients (Fig. 1); air-space consolidation was found in 31 (48.4%) of 64 patients (Fig. 2); and reticulation was found in 43 (67.2%) of 64 patients (Fig. 3). Honeycombing was found in 2 (3.1%) of 64 patients, interlobular septal thickening in 49 (76.6%) of 64 patients, thickening of bronchovascular bundles in 43 (67.2%) of 64 patients, nonseptal linear opacity in 22 (34.4%) of 64 patients, subpleural curve-linear shadow in 24 (37.5%) of 64 patients, and lower volume loss in 57 patients (89.1%) of 64 patients.

The predominant overall anatomic distribution was peripheral in 61 (95.3%) of 64 patients and peribronchovascular in 47 (73.4%). The predominant overall zonal predominance was lower in 63 patients (98.4%).

Table 3
Frequencies of each CT finding according to anatomic distribution.

CT findings	Number of patients
Ground-glass attenuation	
Central predominance	0/63
Peripheral predominance	56/63
Peribronchovascular predominance	32/63
Diffuse predominance	3/63
Random predominance	2/63
Dependent predominance	1/63
Air-space consolidation	
Central predominance	0/31
Peripheral predominance	27/31
Peribronchovascular predominance	29/31
Diffuse predominance	0/31
Random predominance	0/31
Dependent predominance	2/31
Reticulation	
Central predominance	0/43
Peripheral predominance	30/43
Peribronchovascular predominance	16/43
Diffuse predominance	0/43
Random predominance	0/43
Dependent predominance	0/43

The frequencies of each CT finding according to anatomic distribution are listed in Table 3. Ground-glass attenuation had peripheral predominance in 56 (88.9%) of 63 patients, and peribronchovascular predominance in 32 (50.8%) of 63 patients. Air-space consolidation had peripheral predominance in 27 (87.1%) of 31 patients, and peribronchovascular predominance in 29 (93.5%) of 31 patients. Reticulation had peripheral predominance in 30 (69.8%) of 43 patients and peribronchovascular predominance in 16 (37.2%) of 43 patients.

Table 4 shows the final radiologic diagnosis as follows: 1 (1.6%) of 64 patients had UIP, no patient had possible UIP, and 63 (98.4%) of 64 patients had inconsistent UIP. Of the 63 patients, 35 (55.6%) had nonspecific interstitial pneumonia (NSIP), 4 (6.3%) had OP, 22 (34.9%) had OP with fibrosis, and 2 (3.2%) were unclassifiable (Fig. 4).

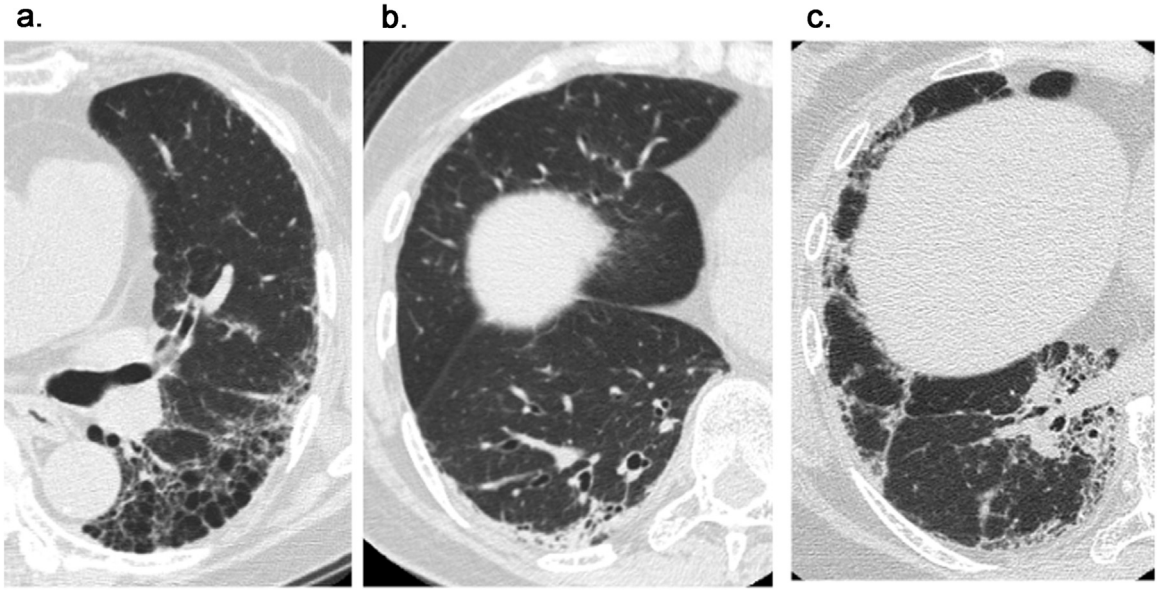

Fig. 3. Reticular opacities. (a) Thin-section CT scan of the right lung in a 64-year-old woman with ARS-ILD (KS) shows reticular opacities in peripheral areas. (b) Thin-section CT scan of the right lung in a 59-year-old man with ARS-ILD (Jo-1) demonstrates reticular opacities in both peripheral and peribronchovascular regions. (c) Thin-section CT scan of the left lung in a 64-year-old woman with ARS-ILD (EJ) presents reticular opacities in both peripheral and peribronchovascular areas.

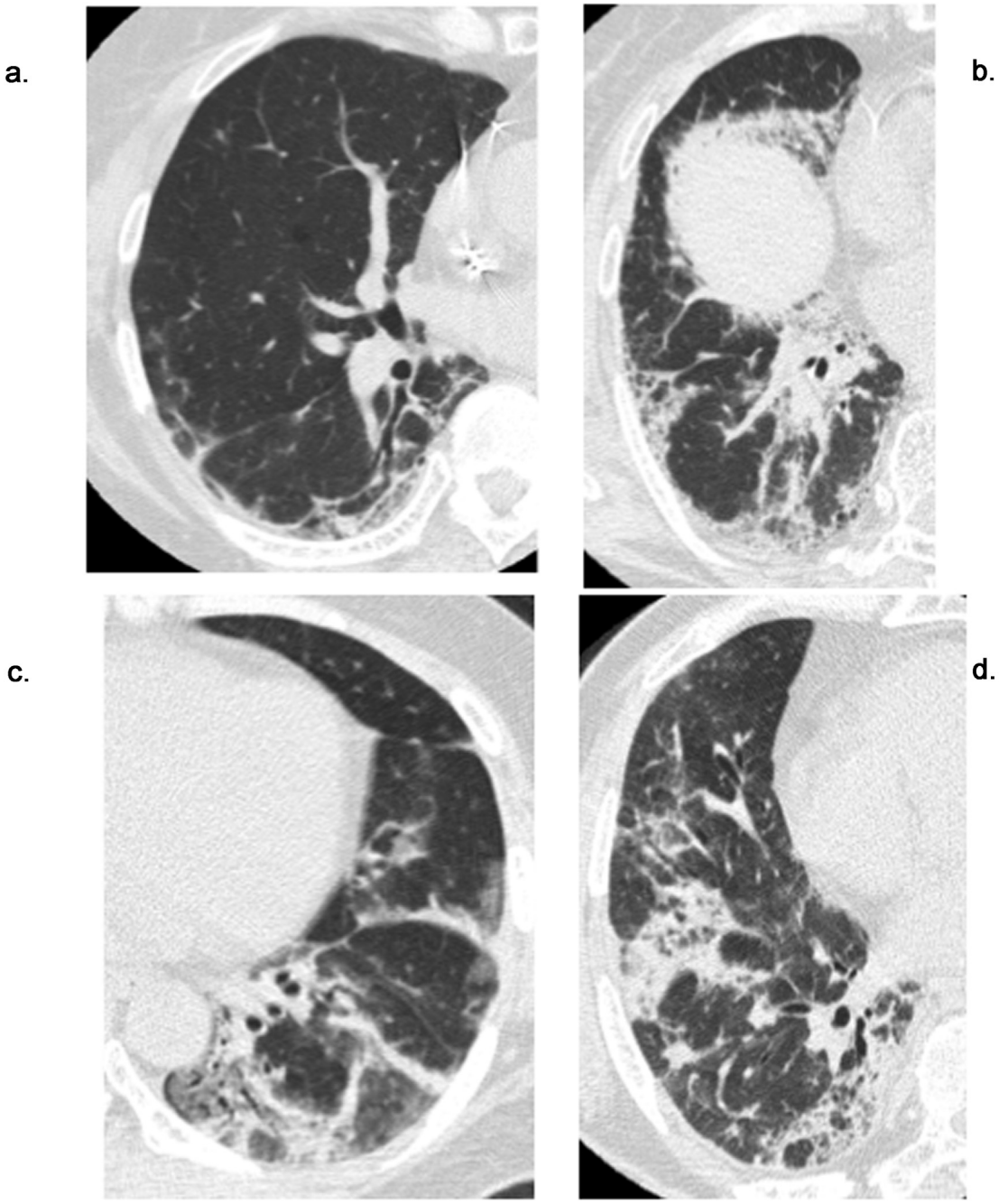

Fig. 4. Ragiologic diagnosis. OP with fibrosis. (a) Thin-section CT scan of the right lung in a 67-year-old woman with ARS-ILD (EJ) shows NSIP pattern. (b) Thin-section CT scan of the right lung in a 72-year-old woman with ARS-ILD (EJ) presents NSIP pattern. (c) Thin-section CT scan of the left lung in a 56–year-old woman with ARS-ILD (Jo-1) demonstrates OP with fibrosis pattern. (d) Thin-section CT scan of the right lung in a 66-year-old man with ARS-ILD (PL-12) depicts OP with fibrosis pattern.

Table 4
Final radiologic diagnosis.

CT pattern	Number of patients
UIP pattern	1/64
Possible UIP pattern	0/64
Inconsistent UIP pattern	63/64
NSIP pattern	35/63
OP pattern	4/63
Organized ALI/OP with fibrosis pattern	22/63
Other/Cannot classify	2/63

UIP, usual interstitial pneumonia; NSIP, non-usual interstitial pneumonia; OP, organizing pneumonia; ALI, acute lung injury.

4. Discussion

In this study, we evaluated the chest CT images of 64 patients with anti-ARS-ILD, and found the 3 following characteristic findings: 1) the distribution of opacities was predominantly lower lobe, peripheral, and/or peribronchovascular, 2) only a few patients manifested honeycombing, and 3) OP with fibrosis was seen in one-third of patients.

Regarding the distribution of opacities, both reticulation and consolidation were likely to occur in lower and peripheral and/or peribronchovascular areas. Moreover, consolidation occurred strongly in peribronchovascular areas. Air-space consolidation on CT is a pathologic reflection of intraluminal organization,

and ground-glass attenuation is associated with lymphocytic infiltration of alveolar septa [9]. Therefore, our findings indicate that both luminal organization and infiltrated alveolar septa occurred in either the peripheral or peribronchovascular pulmonary regions.

Regarding the rare occurrence of honeycombing, although fibrosis in anti-ARS-ILD manifests as reticulation, it may not progress to honeycombing. Therefore, although we applied the IPF guidelines to them, they almost enter either possible UIP or inconsistent UIP pattern.

Regarding the patients who had OP with fibrosis, many patients with anti-ARS-ILD have been reported to have findings consistent with OP with fibrosis [7], and this pattern was described in the ATS/ERS/JRS/ALAT guidelines Therefore, we interpreted OP with fibrosis as a specific pattern. Characteristic CT findings are regions of airspace consolidation bilaterally that show prominent loss of volume, and distribution predominantly in the basal segments. Regarding the patients which have OP with fibrosis, The IIP guidelines [18] describe a group of patients with a condition that exacerbates relatively quickly, is resistant to therapy, and has CT manifestations of reticulations inside the opacities of OP. Some investigators have reported that some patients with OP on chest CT had poor outcomes [19–21]. In addition, there have been previous reports that patients with antisynthetase syndrome often have this pattern [18,22].

In some patients with antisynthetase syndrome, there seems to be a close association between CT manifestations of OP and acute or subacute exacerbation, and the exacerbation due to tapering the dosage of immunosuppressive agents and steroids. Therefore, a large number of anti-ARS-ILD patients should be studied using precise radiologic-pathologic correlations and by reviewing the outcomes and course of the disease over time.

There were several limitations to this study. First, the κ values of the 2 radiologists were relatively low, possibly because the bias in answer to the items of each observer was too strong, matching rate of two people was high, but κ values came out low calculation. Therefore, we decided to use a third observer to make the final decisions. Second, since this was a retrospective study, there were various time phases on chest CT at the time of their first visit. The patients were initially seen at the Department of Respiratory Medicine with a chief complaint of respiratory symptoms such as shortness of breath and dry cough, or an abnormal shadow was seen on a conventional chest radiograph during evaluation for connective tissue disease or during a routine medical examination. A study that includes more patients can overcome this limitation. Third, despite excluding patients with other diseases manifesting with chest CT abnormalities, we could not exclude environmental factors, such as smoking and occupational hazards, associated with chest CT abnormalities. There is a limit that changes in all of the images were described in ARS; however a study that includes more patients can overcome this limitation.

In conclusion, the characteristic CT findings of patients with anti-ARS-ILD were areas of ground-glass attenuation and reticulation, predominantly distributed as lower and peribronchovascular lesions, which is compatible with fibrosing NSIP. One-third of our patients had CT findings of OP with fibrosis.

Key points

1. Antibodies against ARS have been shown to be highly specific for polymyositis and dermatomyositis (PM/DM) and strongly associated with interstitial lung diseases (ILD).
2. Anti-ARS-antibody-positive (anti-ARS)-ILD was not uncommon in patients with idiopathic interstitial pneumonias, and patients with anti-ARS-ILD had common clinical pulmonary manifestations, regardless of the presence of PM/DM.
3. The characteristic computed tomography (CT) findings of patients with anti-ARS-ILD were areas of ground-glass attenuation and reticulation, predominantly distributed as lower and peribronchovascular lesions, which were compatible with fibrosing nonspecific interstitial pneumonia.
4. One-third of our patients with anti-ARS-ILD had CT findings of organizing pneumonia with fibrosis.

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